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CLINICAL STUDY ON RECURRENCE IN BLADDER CANCER PATIENTS UNDERGOING TOTAL CYSTECTOMY —STATISTICAL ANALYSIS OF FACTORS RELATED TO RECURRENCE—

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A clinico-pathological study was performed retrospectively for 77 patients undergoing total cystectomy for primary transitional cell carcinoma of the urinary bladder between 1981 and 1995 to clarify the mode of recurrence, the risk factors which may affect recurrence following cystectomy and prognostic factors. Postoperative recurrence was recognized in 27 (35.1%) out of 77 patients and the one-, two- and three-year non-recurrent rates by the Kaplan-Meier method were 75.3, 64.9% and 63.3%, respectively. The duration from cystectomy to recurrence was 1 to 102 months with a mean of 12.1 months, and approximately 92.6% of recurrence occurred within two years. Among 27 patients with recurrence, pelvic recurrence, distant metastasis, both of them and urethral recurrence were recognized in 6 (22.2%), 18 (66.7%), 1 (3.7%) and 2 (7.4%), respectively as the first site of recurrence. The overall one-, three- and five-year cause-specific survival rates of the 77 patients were 84.7, 71.1% and 65.6%, respectively. Of the 27 patients with recurrence, 25 (92.6%) died of bladder cancer. Of the factors related to recurrence or prognosis, pathological stage, lymphatic invasion, venous invasion, type of infiltration and lymph node metastasis but not pathological grade or adjunctive chemotherapy were significant risk factors for recurrence and prognostic factors in univariate analysis. However, lymphatic invasion was the only significant risk factor for recurrence and prognosis in multivariate analysis using Cox's proportional hazard model.

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Key words: Bladder tumor, Cystectomy, Risk factor for recurrence

INTRODUCTION

Radical total cystectomy is now the standard treatment modality for invasive bladder cancer. However the therapeutic effect of surgery alone still remains unsatisfactory. Therefore, in order to obtain further improvement in prognosis, it is important to predict the cases with a high probability of postoperative recurrence, and to establish effective adjunctive chemotherapy.

We performed a clinico-pathological investigation to clarify the mode of recurrence, the factors which may contribute to recurrence after total cystectomy and the prognostic factors.

MATERIALS AND METHODS

Between August 1981 and December 1995, a total of 87 patients underwent total cystectomy for primary bladder cancer at Aichi Medical University Hospital. The histological type was transitional cell carcinoma (83 patients), squamous cell carcinoma (2 patients) and adenocarcinoma (2 patients). A clinical study was carried out retrospectively on the mode of recurrence and factors related to postoperative

recurrence or prognosis for the 77 patients who had transitional cell carcinoma with preserved histological specimens and clinical records. Pathologically relevant items were described on the basis of General Rules for Clinical and Pathological Studies on bladder cancer edited by the Japanese Urological Association and the Japanese Society of Pathology¹⁾.

There were 63 males and 14 females. The age distribution ranged from 31 to 76 years (median age 62.6 years). The correlation between pathological grade and stage was shown in Table 1. Of the 77 patients, pelvic lymph node dissection was performed on 71 patients and urethrectomy was performed on 42 patients (28 males and 14 females). However, navicular urethra was not extirpated in males as a rule. Fifty-three patients received chemotherapy alone or combined with radiotherapy before and/or after cystectomy. Among them, 6 patients received only preoperative neoadjuvant chemotherapy by intra-arterial infusion of cis-platinum (CDDP) and doxorubicin (ADM) or tetrahydropyranil-doxorubicin instead of ADM, and postoperative adjuvant chemotherapy was performed alone in 42 patients. Furthermore the remaining 5 patients were given

Table 1. Correlation between pathological grade and stage

	No. pts.	Grade		
		1	2	3
pTis	3	0	0	3
pTa	8	1	7	0
pT1	18	0	11	7
pT2	15	0	6	9
pT3a	9	0	3	6
pT3b	15	0	6	9
pT4	9	0	2	7
Total	77	1	35	41

both neoadjuvant intra-arterial and adjuvant chemotherapy. The regimens of adjuvant chemotherapy consisted of cyclophosphamide, ADM and CDDP (CAP) in 5 patients, methotrexate (MTX), vinblastin (VBL), ADM and CDDP (MVAC) in 16 patients, CDDP, MTX and VBL (CMV) in 8 patients, CDDP in 2 patients and tegafur in 11 patients. Of 11 patients who received neoadjuvant intra-arterial chemotherapy, 8 received simultaneous radiotherapy. Of the 53 patients with chemotherapy, 34 (64.2%) showed a high stage not less than pT2, whereas 14 (58.3%) of the 24 patients without chemotherapy had pT2 or higher stage tumors. The follow-up duration ranged from 9 to 172 months with an average of 87.7 months. The mode of recurrence was classified into local recurrence in pelvic cavity, distant metastasis to remote organ or extra-regional lymph node, urethral recurrence and recurrence in upper urinary tract. As related factors which may contribute to recurrence, seven factors, namely pathological grade (G), pathological stage (pT), lymphatic invasion (pL), venous invasion (pV), type of infiltration (INF), regional lymph node metastasis (pN) and adjunctive chemotherapy were selected.

Non-recurrent rate, cause-specific survival rate and actuarial survival rate were calculated by the Kaplan-Meier method. The statistical significance of

difference was analyzed based on the generalized Wilcoxon test or Logrank test, and differences with a $p < 0.05$ were considered significant. In order to assess the significance of each factor which may affect recurrence or survival rate, multivariate analysis was done using Cox's proportional hazard model with the Statistical Analysis System program. For evaluation of the non-recurrent rate or survival rate, the starting point was designated as the day of cystectomy and the end point was the last day of follow-up, September 30, 1996.

RESULTS

1. Recurrence: Postoperative recurrence was recognized in 27 (35.1%) of the 77 patients. The interval from operation to recurrence was 1 to 102 months with a mean of 12.1 months; recurrence was found within one year in 18 (66.7%) and within two years in 25 (92.6%). One patient with recurrence at the time of 102 months after cystectomy for carcinoma in situ had a recurrent tumor in the anterior urethra. Fig. 1 shows the non-recurrent curve for all the cases; the one-, two- and three-year non-recurrent rates were 75.3, 64.9% and 63.3%, respectively.

2. Mode of recurrence: Table 2 shows the first site

Table 2. Mode of recurrence after total cystectomy

First site of recurrence	No. pts./total (%)
1) Local recurrence alone	6/77 (7.8)
2) Distant metastasis alone	18/77 (23.4)
① Remote organ alone	15/77 (19.5)
Bone	6
Lung	2
Bone plus lung	4
Bone plus liver	1
Lung plus brain	1
Pleura	1
② Extra-regional node alone	3/77 (3.9)
3) Local plus distant	1/77 (1.3)
4) Urethral recurrence	2/35 (5.7)

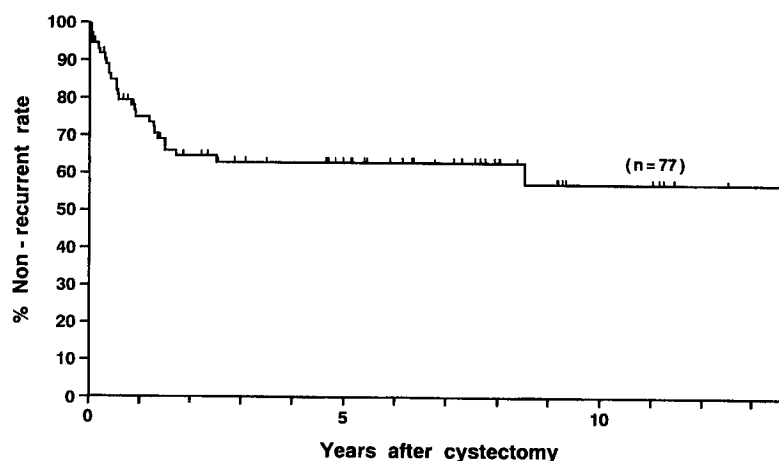


Fig. 1. Overall non-recurrent curve.

of postoperative recurrence. Distant metastasis to remote organs alone occurred in 15 patients, extra-regional lymph node metastasis alone in 3, local recurrence in pelvic cavity alone in 6 and both distant organ metastasis and local recurrence in 1. An incurative operation was the cause of local recurrence in 3 of the 7 patients, while the remaining 4 had recurrence despite appropriate operation. Urethral recurrence was recognized in two (5.7%) of the 35 male patients without removal of anterior urethra, but none had recurrence in the upper urinary tract. Furthermore, final distant metastasis to remote organs was observed in 21, extra-regional lymph node metastasis in 13, local recurrence in 16 and urethral recurrence in 3 throughout the total course of the disease. Among 16 patients with local recurrence, a high probability of recurrence was predicted in 7 because of incurative operation and the other 9 had local recurrence in spite of no evidence of microscopic lymph node involvement. Fourteen (87.5%) of the 16 patients with local recurrence also had metastasis to either distant organs or extra-regional lymph nodes.

3. Correlation between the clinico-pathological factors and recurrence:

1) Pathological grade (G): Among 77 patients with transitional cell carcinoma, 9 (25.7%) of 35 with G2 tumors and 18 (43.9%) of 41 with G3 tumors showed recurrence. One patient with G1 tumor had no recurrence. The one-, two- and three-year non-recurrent rates were 81.3, 77.9% and 74.2% for G2 tumors and 69.8, 53.7% and 53.7% for G3 tumors, respectively. However, no significant difference was recognized between G2 and G3 tumors.

2) Pathological stage (pT): Recurrence was recognized in 1 (9.1%) of 11 patients with pTis/pTa, 3 (16.7%) of 18 with pT1, 5 (33.3%) of 15 with pT2, 3 (33.3%) of 9 with pT3a, 11 (73.3%) of 15 with pT3b and 4 (44.4%) of 9 with pT4. The one-, two- and three-year non-recurrent rates were all 100% for pTis/pTa, 87.5, 81.3% and 81.3% for pT1, 78.6,

Table 3. Correlation between lymphatic invasion, venous invasion or pelvic lymph node metastasis and recurrence

	No. Pts.	Recurrence (%)		Mode of recurrence		
		Negative	Positive	PR	DM	UR
pL-	44	39 (88.6)	5 (11.4)	1	3	1
+	33	11 (33.3)	22 (66.7)	1	21	0
pV-	59	46 (78.0)	13 (22.0)	1	11	1
+	18	4 (22.2)	14 (77.8)	1	13	0
pN-	56	42 (75.0)	14 (25.0)	1	12	1
+	15	2 (13.3)	13 (86.7)	1	12	0
×	6	4 (100)	0 (0)	0	0	0

UR; urethral recurrence, PR; pelvic recurrence, DM; distant metastasis.

64.3% and 64.3% for pT2, 77.8, 64.9% and 64.9% for pT3a, 43.1, 28.7% and 21.5% for pT3b and 66.7, 50.0% and 50.0% for pT4, respectively. A significant difference was demonstrated in the non-recurrent rate between each stage group ($p=0.0005$), and the pT3b group showed a significantly lower non-recurrent rate than the pTis/pTa, pT1, or pT2 group ($p=0.0001$, $p=0.0002$ or $p=0.0086$).

3) Lymphatic invasion (pL): Twenty-three (66.7%) of 33 patients with positive pL and 5 (11.4%) of the 44 with negative pL showed recurrence (Table 3). The one-, two- and three-year non-recurrent rates were 52.8, 33.0% and 29.7% for positive pL, whereas 92.6, 90.0% and 90.0% for negative pL, respectively and the positive pL group showed a significantly low non-recurrent rate compared with the negative pL group ($p<0.0001$) (Fig. 2A).

4) Venous invasion (pV): Fourteen (77.8%) of the 18 patients with positive pV and 13 (22.0%) of the 59 with negative pV showed recurrence (Table 3). The one-, two- and three-year non-recurrent rates were 33.7, 27.0% and 20.0% for positive pV and 87.5, 76.0% and 76.0% for negative pV, respectively, and a significant difference was recognized between them

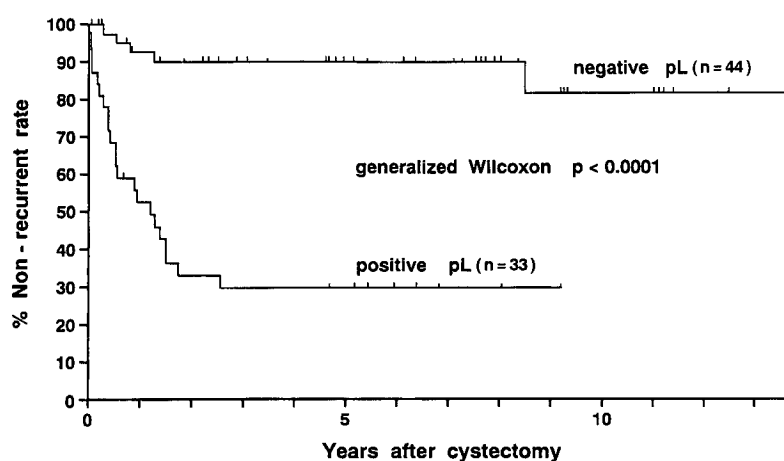


Fig. 2A. Non-recurrent curves according to lymphatic invasion.

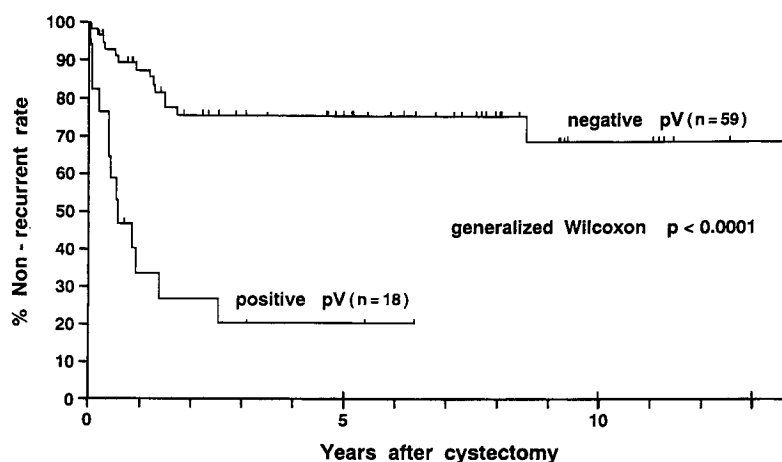


Fig. 2B. Non-recurrent curves according to venous invasion.

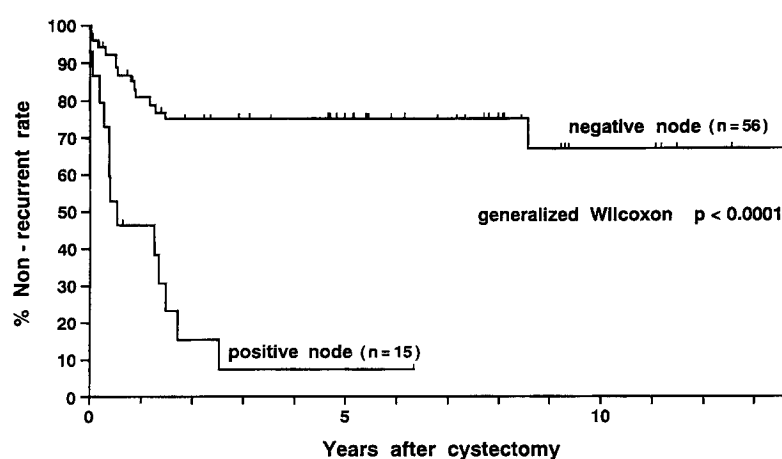


Fig. 2C. Non-recurrent curves according to pelvic lymph node metastasis.

($p < 0.0001$) (Fig. 2B).

5) Type of infiltration (INF): Among the 77 patients, 2 (9.1%) of 22 with INF- α , 8 (32.0%) of the 25 with INF- β and 17 (56.7%) of the 30 with INF- γ showed recurrence. The one-, two- and three-year non-recurrent rates were all 95.2% for INF- α , 73.1, 63.3% and 63.3% for INF- β and 63.0, 44.4% and 40.4% for INF- γ , respectively, the difference among each INF group being significant ($p = 0.0019$).

6) Regional lymph node metastasis (pN): Recurrence was found in 13 (86.7%) out of 15 patients with positive pN and in 14 (25%) out of 56 patients with negative pN (Table 3). Furthermore, 1 (50%) of the 2 patients with pN1 and 12 (92.3%) of the 13 patients with pN2-N3 showed recurrence. The one-, two- and three-year non-recurrent rates were 46.7, 15.6% and 7.8% for positive pN, and 81.4, 75.4% and 75.4% for negative pN, respectively, the difference between the positive and negative pN being significant ($p < 0.0001$) (Fig. 2C).

7) Adjunctive chemotherapy: Twenty-one (39.6%) of the 53 patients receiving chemotherapy and 6 (25%) of the 24 not receiving chemotherapy showed recurrence. The one-, two- and three-year non-recurrent rates were 72.9, 62.6% and 60.3%,

respectively, for the chemotherapy group, and 81.9, 70.9% and 70.9%, respectively, for the group without chemotherapy, there being no significant difference between the two groups. Furthermore, no significant difference was noted for the patients with a high stage of more than pT2.

4. Multivariate analysis of factors related to recurrence (Table 4): Multivariate analysis was performed to examine the degree of contribution to recurrence of the five factors, i.e., pT, pL, pV, INF and pN, which showed a significant difference in

Table 4. Multivariate analysis of risk factor influencing recurrence (by Cox's proportional hazard model)

Variable	Partial regression coefficient	S.E.	P value	T value	Risk ratio
p Stage	0.144805	0.69856	0.8358	0.2072907	1.156
pL	1.825517	0.72962	0.0123	2.5020106	6.206
pV	0.667958	0.47058	0.1558	1.4194355	1.950
INF	0.018053	0.45067	0.9680	0.0400581	1.018
pN	0.246951	0.41935	0.5559	0.5888899	1.280

$P < 0.05$; Statistically significant, S.E.; Standard error, T value; Partial regression coefficient/standard error.

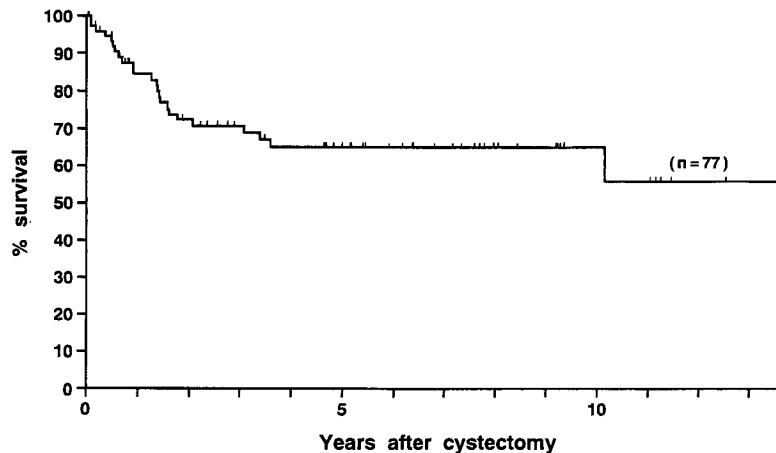


Fig. 3. Overall cause-specific survival curve.

univariate analysis. To compare the degree of importance of each factor as a risk factor for recurrence, we employed the *t* value which means each partial regression coefficient divided by each standard error. The *t* values were in the decreasing order of pL, pV, pN, p Stage and INF, indicating that these factors contributed to recurrence in this order. Namely pL was the most important factor for recurrence and pL alone showed a significant difference ($p=0.0123$). Moreover, the positive pL group showed a 6.206 times higher hazard ratio than the negative pL group.

5. Prognosis: The overall one-, three- and five-year actuarial survival rates were 76.5, 62.8% and 54.7%, respectively. The overall one-, three- and five-year cause-specific survival rates were 84.7, 71.1% and 65.6%, respectively (Fig. 3). Moreover in statistical analysis of factors affecting the cause-specific survival rate, pT, pL, pV, INF and pN were significant prognostic factors in univariate analysis, but only pL was a significant prognostic factor in multivariate analysis. Of 27 patients with recurrence, 25 (92.6%) died of bladder cancer and the other two died of gastric cancer or suffocation. Almost 80% of the deaths due to tumor recurrence occurred during the first 2 years following cystectomy and 8% of the cancer deaths occurred in the third and fourth year after surgery, respectively. Furthermore, 23 (92%) of the 25 deaths due to bladder cancer occurred within one year after identification of recurrence.

DISCUSSION

Radical total cystectomy is the standard treatment for locally invasive bladder cancer, but postoperative recurrence frequently occurs. Although there is some variability in the reported recurrence rate after radical total cystectomy for bladder cancer because of different clinico-pathological backgrounds of patients, the incidence of recurrence following cystectomy is about 20 to 30% on the whole²⁻⁵ In

the present study, recurrence was noted in 27 (35.1%) of the 77 patients undergoing total cystectomy.

Most of the patients generally showed recurrence within two years^{2,5,6}. In our series, 18 (66.7%) of the 27 patients showed recurrence within one year and 25 (92.6%) within two years. Thus, the patient should be observed for recurrence for at least two years following cystectomy with a particular attention.

Many investigators⁷⁻⁹ have reported that distant metastasis was more important than pelvic recurrence. Furthermore, other authors^{2,5} have reported that approximately 60 to 70% of the patients having postoperative recurrence showed distant metastasis as the first site of recurrence, while pelvic recurrence was observed in the other 30 to 40%. In general, the incidence of pelvic recurrence as the first site of progression among all patients undergoing total cystectomy was nearly 10% or less in most series^{6,10-13}. When the cases with evidence of macroscopic residual tumor at operation are excluded, tumor spillage, urethral remnant and microscopic pelvic metastasis are considered to be the causative factors for pelvic recurrence¹⁰. Tsutsumi et al.² analyzed 15 patients with pelvic recurrence in detail and concluded that unless the tumor was demonstrated in the surgical margin, the incidence of local recurrence was low and the rate of distant metastasis was rather high. In our series as well, pelvic recurrence was the first site of relapse in 7 (9.1%) of the 77 patients undergoing cystectomy; pelvic recurrence alone was found in 6 (22.2%) of the 27 patients with recurrence and distant metastasis alone in 18 (66.7%). However, if we exclude the two patients with either macroscopic evidence of residual tumor at surgery or incurative operation due to multiple regional lymph node metastasis, pelvic recurrence was observed in only 4 (16%) of the 25 patients, thus, supporting the view of Tsutsumi et al.² or Roehrborn et al.⁴ that the majority of relapses were systemic regardless of the initial extent of

disease.

Many authors have referred to the correlation between pathological grade, pathological stage, vascular invasion, type of infiltration, regional pelvic lymph node metastasis or adjunctive chemotherapy and recurrence. Generally the recurrence rate is greater in a high grade tumor than in a low grade tumor¹⁰⁾. In our series, recurrence was found in 25.7% of the patients with a grade 2 tumor and in 43.9% of those with a grade 3 tumor. The patients with a grade 3 tumor showed a slightly higher incidence of recurrence in comparison with those with a grade 2 tumor, but the difference was not significant.

The recurrence rate was higher at a higher pathological stage. The recurrence rate is low up to stage pT1 tumor. In our small series, the recurrence rate was as high as 33.3% in stage pT2 tumor, although Komatsu et al.³⁾ observed a low recurrence rate of only 8%. Lerner et al.⁶⁾ observed a significantly higher risk of recurrence for patients with a pathological tumor stage greater than P3a. Soloway et al.¹⁴⁾ also found a high incidence of recurrence in patients with pT4–T4 regardless of their lymph node status. In general, the recurrence rate is high in patients with tumors infiltrating to the deep muscle of the bladder wall, especially with advanced stage of pT3b or higher.

Lerner et al.⁶⁾ found lymphovascular invasion at the site of the primary tumor in 76 out of 132 patients with nodal involvement, but it was not a significant predictor of recurrence. In our series, lymphatic invasion was a risk factor for recurrence both in univariate and multivariate analysis and the positive pL group showed a 6.206 times higher hazard ratio than the negative pL group.

There have been many reports on the correlation between nodal metastasis and recurrence. In general, many investigators observed a rather high recurrence rate of 60 to 80% in patients with positive nodes^{2,4,6,7,15,16)} and in our series as well, 13 (86.7%) of 15 patients with positive node showed recurrence. Approximately 80 to 90% of postoperative recurrence was accompanied with distant metastasis^{2,6,8)}

Skinner⁸⁾ demonstrated pelvic recurrence in only 2 (9.1%) of the 22 patients with recurrence as the first site of relapse, while the remaining 20 (90.9%) had widespread dissemination, usually presenting with clinical evidence of liver, bone or lung metastasis and Lerner and associates⁶⁾ also reported that 15 (17%) out of 89 patients with recurrence, showed pelvic recurrence alone as the first site of progression, whereas the other 74 (83%) had distant metastasis. Tsutsumi et al.²⁾ also observed the same high incidence of distant metastasis and, thus, concluded that lymph node metastasis in bladder cancer indicated widespread disease, the significance of

extended lymphadenectomy thus being small. In our series as well, local recurrence alone was recognized in one (7.7%) of the 13 patients with relapse, with positive node, but the other 12 (92.3%) had distant metastasis. Thus, regional nodal spread may imply the presence of distant micrometastasis that is probably present at the time of surgery in the majority of patients¹⁵⁾. In general lymph node involvement may indicate systemic metastatic disease and the need for adjuvant systemic therapy. However, on the contrary Skinner⁸⁾ reported that a meticulous pelvic node dissection can cure some patients with metastasis to a few pelvic nodes. Several reports have been presented concerning the correlation between the number of involved nodes and recurrence. Tsutsumi et al.²⁾ reported that among 10 patients alive without recurrence despite lymph node metastasis, 8 had nodal involvement of less than 3 nodes. Therefore, patients with two or less positive node may be curable by cystectomy. Nishio et al.¹⁶⁾ reported that the recurrence rate was 41% in patients with less than 4 metastasized nodes and distant metastasis was significant, whereas in those with 4 or more positive nodes the recurrence rate was 83% and not only distant metastasis but also pelvic recurrence were observed with a high incidence. On the other hand, Lerner et al.⁶⁾ reported that the finding of more than 5 positive nodes was a significant risk factor of recurrence. In our series, among 15 patients with node metastasis, 1 (50%) of the 2 in the pN1 group and 12 (92.3%) of the 13 in the pN2–N3 group showed recurrence. These findings indicate that patients with even a few positive nodes have a high possibility of recurrence.

There have been some different reports on the effectiveness of chemotherapy to decrease the risk of recurrence. Stöckle et al.¹⁷⁾ reported that adjuvant chemotherapy with the regimen of M-VAC after radical cystectomy for patients with tumor stage pT3b, pT4a and/or pelvic lymph node involvement caused a significant decrease in the risk of tumor recurrence. Skinner et al.¹⁸⁾ reported that the prevention of recurrence by chemotherapy was most evident for the first three years in cases with N1, and recurrence occurred rapidly in those with more than N2. On the contrary, Lerner et al.⁶⁾ observed no significant difference in recurrence between surgery alone and surgery plus adjuvant chemotherapy. We could not evaluate the effectiveness of adjuvant or/and neoadjuvant chemotherapy sufficiently owing to the small number and different backgrounds of the patients. Considering the high incidence of distant metastasis, compared with low incidence of pelvic recurrence following cytectomy, systemic chemotherapy seems to be a logical approach to eradicate micrometastasis, and thus in order to estimate the effectiveness of adjunctive chemotherapy properly

and objectively, prospective randomized controlled trials are essential. In our series, 25 (92.6%) out of 27 patients with recurrence died of bladder cancer irrespective of adjunctive therapy. Postoperative recurrence has almost always lead to cancer death and therefore prevention of recurrence is extremely important. However, in recent years cystectomy combined with pre- and/or postoperative chemotherapy for deeply invasive tumor has resulted in a good clinical outcome, and further studies concerning the impact of chemotherapy on recurrence are needed.

CONCLUSION

In the present study, postoperative recurrence occurred in 27 (35.1%) of the 77 patients undergoing total cystectomy for transitional cell carcinoma of the bladder. Approximately 70% of the first recurrence were distant metastasis and the incidence of local recurrence was rather small. pT, pL, pV, INF and pN were significant risk factors for recurrence or prognostic factors in univariate analysis, but only pL showed a significant difference as a risk factor for recurrence or prognosis in multivariate analysis. Furthermore, pL revealed the highest hazard ratio.

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膀胱癌に対する膀胱全摘除術後の再発に関する臨床病理学的研究
—再発寄与因子の統計学的分析—

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1981年から1995年までの間に愛知医科大学付属病院において膀胱全摘除術が行われた原発性膀胱移行上皮癌77例を対象に術後の再発様式、再発および予後因子の臨床的検討を行った。77例中27例（35.1%）に再発が認められ、1, 2, 3年非再発率はおおの75.3, 64.9, 63.3%であった。手術後再発までの期間は平均12.1カ月で、27例中25例（92.6%）が2年以内に再発した。初回再発部位として27例中、骨盤内再発のみ6例（22.2%）、遠隔転移のみ18例（66.7%）、骨盤内再発および遠隔転移1例（3.7%）、尿道再発2例（7.4%）であった。遠隔臓器転移の部位としては骨が最も多く、ついで肺の順であった。全体的原因特異的生存率は1年84.7%, 3年71.1%, 5年65.6%であり、

27例中25例（92.6%）が膀胱癌死した。再発もしくは予後関連因子として組織学的異型度、組織学的深達度、リンパ管侵襲、静脈侵襲、組織学的浸潤増殖様式、所属リンパ節転移、補助化学療法をとりあげ、再発および予後との関係について単変量およびCoxの比例ハザードモデルを用いた多変量解析を行った。その結果、深達度、リンパ管侵襲、静脈侵襲、浸潤増殖様式、所属リンパ節転移は、単変量解析では有意な再発危険因子および予後因子であったが、多変量解析ではリンパ管侵襲のみが有意な再発および予後に対する危険因子であった。

（泌尿紀要 45 : 317-324, 1999）